WEST Search History

DATE: Monday, December 15, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L2	L1 and crystal$8	8	L2
L1	pneumoniae and acyl carrier protein synthase	28	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 8 of 8 returned.

☐ 1. Document ID: US 20030068802 A1

L2: Entry 1 of 8 File: PGPB Apr 10, 2003

PGPUB-DOCUMENT-NUMBER: 20030068802
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030068802 A1

TITLE: Use of streptococcus pneumoniae acyl carrier protein synthase crystal structure in diagnostics, antimicrobial drug design, and biosensors

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chirgadze, Nicholas Yuri	Indianapolis	IN	US	
Briggs, Stephen Lyle	Indianapolis	IN	US	
Zhao, Genshi	Indianapolis	IN	US	
McAllister, Kelly Ann	Indianapolis	IN	US	

US-CL-CURRENT: 435/193; 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020142401 A1

L2: Entry 2 of 8 File: PGPB Oct 3, 2002

PGPUB-DOCUMENT-NUMBER: 20020142401
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020142401 A1

TITLE: Isolated gene for methylmalonyl CoA epimerase and uses thereof

PUBLICATION-DATE: October 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Santi, Daniel	San Francisco	CA	US	
Dayem, Linda	Belmont	CA	US	
Kealey, James	San Rafael	CA	US	

US-CL-CURRENT: 435/76; 435/252.3, 435/320.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

3. Document ID: US 6656703 B1

L2: Entry 3 of 8 File: USPT Dec 2, 2003

US-PAT-NO: 6656703
DOCUMENT-IDENTIFIER: US 6656703 B1

TITLE: High throughput screen for inhibitors of fatty acid biosynthesis in bacteria

DATE-ISSUED: December 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Murphy; Christopher	Upton	MA		
Youngman; Philip	Boston	MA		

US-CL-CURRENT: 435/32; 435/183, 435/243, 435/6, 435/7.2, 530/350, 536/24.1, 536/24.32

ABSTRACT:

Methods for identifying compounds that are inhibitors of bacterial fatty acid biosynthesis are disclosed. Such compounds can be used as lead compounds in methods for preparing antibacterial agents for treating bacterial infections (e.g., in humans, animals, and plants). Inhibitors of bacterial fatty acid synthesis can also be tested for their ability to inhibit synthesis of acylated homoserine lactones. Compounds that inhibit synthesis of acylated homoserine lactones can be used as inhibitors of bacterial virulence. The disclosed methods allow for high throughput screening of libraries of test compounds.

13 Claims, 8 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 6

4. Document ID: US 6583275 B1

L2: Entry 4 of 8 File: USPT Jun 24, 2003

US-PAT-NO: 6583275
DOCUMENT-IDENTIFIER: US 6583275 B1

TITLE: Nucleic acid sequences and expression system relating to Enterococcus faecium for diagnostics and therapeutics

DATE-ISSUED: June 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Doucette-Stamm; Lynn A.	Framingham	MA		
Bush; David	Somerville	MA		

US-CL-CURRENT: 536/23.1; 435/243, 435/320.1, 435/325, 435/6, 536/24.3, 536/24.32

ABSTRACT:

The invention provides isolated polypeptide and nucleic acid sequences derived Enterococcus faecium that are useful in diagnosis and therapy of pathological

conditions; antibodies against the polypeptides; and methods for the production of the polypeptides. The invention also provides methods for the detection, prevention and treatment of pathological conditions resulting from bacterial infection.

34 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 5. Document ID: US 6515119 B1

L2: Entry 5 of 8 File: USPT Feb 4, 2003

US-PAT-NO: 6515119
DOCUMENT-IDENTIFIER: US 6515119 B1

TITLE: Use of S-ydcB and B-ydcB, essential bacterial genes

DATE-ISSUED: February 4, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fritz; Christian	Natick	MA		
Youngman; Philip	Boston	MA		
Guzman; Luz-Maria	Boston	MA		

US-CL-CURRENT: 536/23.7; 435/252.3, 435/254.2, 435/320.1, 536/23.1

ABSTRACT:

Disclosed are methods for using the essential genes and polypeptides "S-ydcB," found in Streptococcus pneumoniae, and "B-ydcB," found in Bacillus subtilis. These genes and polypeptides, as well as homologs and orthologs thereof, can be used to identify antibacterial agents for treating a broad spectrum of bacterial infections.

19 Claims, 4 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 6. Document ID: US 6503729 B1

L2: Entry 6 of 8 File: USPT Jan 7, 2003

US-PAT-NO: 6503729
DOCUMENT-IDENTIFIER: US 6503729 B1

TITLE: Selected polynucleotide and polypeptide sequences of the methanogenic archaeon, methanococcus jannashii

DATE-ISSUED: January 7, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bult; Carol J.	Bar Harbor	ME		
White; Owen R.	Gaithersburg	MD		
Smith; Hamilton O.	Baltimore	MD		
Woese; Carl R.	Urbana	IL		
Venter; J. Craig	Rockville	MD		

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 536/23.1, 536/23.5

ABSTRACT:

The present application describes selected polynucleotide sequence from the 1.66-megabase pair genome sequence of an autotrophic archaeon, Methanococcus jannaschii, and its 58- and 16-kilobase pair extrachromosomal elements.

107 Claims, 2 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 7. Document ID: US 20030068802 A1

L2: Entry 7 of 8 File: DWPI Apr 10, 2003

DERWENT-ACC-NO: 2003-657574
DERWENT-WEEK: 200362

TITLE: Composition comprising a crystal of isolated Streptococcus pneumoniae acyl carrier protein synthase, for determining the 3-dimensional structure of the enzyme for developing antibacterial enzyme inhibitors

INVENTOR: BRIGGS, S L; CHIRGADZE, N Y ; MCALLISTER, K A ; ZHAO, G

PRIORITY-DATA: 2000US-215577P (June 30, 2000), 2001US-0897645 (June 29, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20030068802 A1	April 10, 2003		158	C12N009/10

INT-CL (IPC): C12 N 9/10; G01 N 33/48; G01 N 33/50; G06 F 19/00

ABSTRACTED-PUB-NO: US20030068802A
BASIC-ABSTRACT:

NOVELTY - A composition (C), comprising a crystal of isolated Streptococcus pneumoniae acyl carrier protein synthase (AcpS) (I), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) an enzyme active site crystal structure (II) comprising 3',5'- adenosine diphosphate (ADP) binding site, as shown in the specification;

(2) isolating (M1) AcpS (I);

(3) isolated (I) produced by M1;

(4) producing (M2) a crystal of S. pneumoniae acyl carrier protein synthase that diffracts X-rays;

(5) a crystal of (I) produced by M2; and

(6) a co-crystal of (I) with a compound.

USE - The crystal of (I) is useful for determining the 3-dimensional structure of (I) (claimed). The 3-dimensional crystal structure of (I) is useful in medical diagnostics to produce antibodies that permit detection of S. pneumoniae both in vitro and in vivo, and therefore accurate diagnosis of infections caused by the bacterium. The 3-dimensional structure of (I) is also useful in pharmaceutical discovery and development to identify and design compounds that inhibit the biochemical activity of AcpS enzyme in bacteria. Structure/activity studies can be used to optimize the inhibitory activity of compounds to develop antibacterial pharmaceutical compounds for the prevention and treatment of bacterial infections in mammals. The 3-dimensional crystal structures can be used to model AcpS, for solving a crystal structure, and for determining the 3-dimensional structure of AcpS enzymes of unknown structure, and for designing a ligand that binds to the active site domain of (I). The crystals of (I) are also useful as biosensors and other applications. The crystals of (I) can be used in the preparation of acyl carrier protein (ACP) analogs or ACP-derivatives, and the manufacture of catalysis of selected products such as for research, pharmaceutical or industrial applications. The crystals are useful as the fabrication material in the process, manufacture and/or production of a microelectronic device e.g. in the formation of 2-dimensional array on a solid support. The crystals can be used as a fabrication mask and/or template for improvements in silicon nano- and micro-fabrication technology.

☐ 8. Document ID: WO 2003027139 A2

L2: Entry 8 of 8 File: DWPI Apr 3, 2003

DERWENT-ACC-NO: 2003-441048
DERWENT-WEEK: 200341

TITLE: Novel crystallized recombinant polypeptides from Staphylococcus aureus, Streptococcus pneumoniae and Helicobacter pylori and which are involved in membrane biosynthesis, useful as targets for pathogenic bacteria

INVENTOR: ALAM, M Z; AWREY, D ; BEATTIE, B ; CANADIEN, V ; DHARAMSI, A ; DOMAGALA, M ; EDWARDS, A ; HOUSTON, S ; KANAGARAJAH, D ; LI, Q ; MANSOURY, K ; MCDONALD, M ; NECAKOV, S ; NG, I ; PINDER, B ; SHELDRICK, B ; VALLEE, F ; VEDADI, M ; VIOLA, C ; WREZEL, O

PRIORITY-DATA: 2001US-343946P (December 27, 2001), 2001US-324449P (September 24, 2001), 2001US-324504P (September 24, 2001), 2001US-326269P (October 1, 2001), 2001US-326887P (October 3, 2001), 2001US-339560P (October 24, 2001), 2001US-337471P (October 25, 2001), 2001US-340000P (October 26, 2001), 2001US-340002P (October 26, 2001), 2001US-340027P (October 26, 2001), 2001US-341767P (December 18, 2001), 2001US-344307P (December 21, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 2003027139 A2	April 3, 2003	E	312	C07K014/195

INT-CL (IPC): C07 K 14/195

ABSTRACTED-PUB-NO: WO2003027139A
BASIC-ABSTRACT:

NOVELTY - A crystallized recombinant polypeptide (I) comprising amino acid sequence of polypeptides from Staphylococcus aureus, Streptococcus pneumoniae, Helicobacter pylori and Pseudomonas aeruginosa and which are involved in membrane biosynthesis, or amino

acid sequences having at least 90 % identity with the polypeptide sequence, where the polypeptide is in crystal form, is new.

DETAILED DESCRIPTION - A crystallized recombinant polypeptide (I) comprises the amino acid sequence of polypeptides (P) involved in membrane biosynthesis, which includes FtsZ cell division protein (FtsZ), (3R)-hydroxymyristol acyl carrier protein dehydratase (FabZ), acyl carrier protein synthase (AcpS), (3-oxoacyl-(acyl-carrier-protein) synthase III (FabH), teichoic acid biosynthesis protein D (TagD), and Spo0B-associated GTP-binding protein (Obg) from S. aureus 3-ketoacyl-acyl-carrier protein reductase (FabG), UDP-N-acetylmuramoylala-nine-D-glutamate ligase (MurD) and L-alanine adding enzyme (UDP-N-acetyl-muramate:alanine ligase) (MurC) from H. pylori, acyl carrier protein synthase (AcpS) from S. pneumoniae, 3-oxoacyl-(acyl-carrier-protein)reductase (FabG) from P. aeruginosa. (I) comprises an amino acid sequence having at least 90 or 95 % identity with the amino acid sequence of (P), or comprises an amino acid sequence encoded by a polynucleotide that hybridize under stringent conditions to the complementary strand of a polynucleotide having a sequence encoding any of (P). (I) is in a crystal form.

INDEPENDENT CLAIMS are also included for:

(1) a sample (II) comprising (P), labeled with a heavy atom, or enriched in nuclear magnetic resonance (NMR) isotope;

(2) a crystallized complex comprising the recombinant polypeptides as above and a co-factor or a small organic molecule, where the complex is in a crystal form;

(3) a host cell comprising a nucleic acid encoding (P), where the culture of the host cell produces 1 mg of the polypeptide/l of culture and the polypeptide is at least one-third soluble as measured by gel electrophoresis;

(4) a composition (C) comprising an isolated, recombinant polypeptide, FabG, AcpS, MurD, MurC, TagD or AcpS as above, its 95 % identical sequence or an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of polynucleotide encoding any of the above polypeptide, where the polypeptide is at least 90 % pure in a sample of the composition;

(5) a composition (III) same as (C), but comprising only FtsZ, FabZ, Obg, FabG or FabH polypeptide;

(6) a complex comprising a polypeptide of (III) and FTSA cell division protein;

(7) a complex comprising polypeptide of (IV) one or more of 50S ribosomal protein (RP) L22, 30S RP S7, 30S RP S5, 50S RP L5, 50S RP L5, 50S RP L6, 50S RP L4, 30S RP S4, 50S RPL3, 50S RP L2, 30S RP S2, RNA polymerase alpha , RNA polymerase beta and beta ';

(8) a complex comprising FabH and leukotoxin LukM and 16 kDa unidentified protein;

(9) a complex comprising FabH and 50S RP L16 and leukotoxin LukM;

(10) a complex comprising FabG and a 25 kDa unidentified protein;

(11) an isolated, recombinant polypeptide comprising at least 90 % identity with FtsZ polypeptide, or an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of polynucleotide encoding FtsZ, where the polypeptide includes Asp at position 155 and/or 354;

(12) an isolated, recombinant polypeptide comprising at least 90 % identity with FabZ polypeptide from S. aureus, or an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of polynucleotide encoding FabZ, where the polypeptide includes Leu at position 15 and Asn at position 113;

(13) an isolated recombinant polypeptide, comprising at least 90 % identity with FabG from H. pylori or an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having a sequence encoding FabG, where the polypeptide includes Cys at position 55;

(14) an isolated, recombinant polypeptide comprising at least 90 % identity with AcpS,

where the polypeptide includes one or more of the amino acid residues at the specified position of the polypeptide: Lys at position 11;

(15) an isolated, recombinant polypeptide, comprising at least 90 % identity with MurD or an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of polynucleotide encoding MurD, where the polypeptide includes Ala at position 16;

(16) an isolated, recombinant polypeptide comprising at least 90 % identity with MurC polypeptide, or an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of polynucleotide encoding MurC, where the polypeptide includes Thr at position 385, Ile at position 427 and Lys at position 429;

(17) an isolated, recombinant polypeptide comprising at least 95 % identity with Obg polypeptide, or an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of polynucleotide encoding Obg, where the polypeptide includes Phe at position 339; and

(18) an isolated, recombinant polypeptide comprising at least 90 % identity with FabG polypeptide, or an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of polynucleotide encoding FabG, where the polypeptide includes Ala at position 58.

ACTIVITY - Antibacterial.

No biological data is given.

MECHANISM OF ACTION - Vaccine.

USE - (I) is useful for designing a modulator for the prevention or treatment of S. aureus, H. pylori, S. pneumoniae, and P. aeruginosa-related disease or disorder. (I) is also useful for identifying small molecules that bind to a recombinant polypeptide. (All claimed.) The structural and functional information of (I) aid in the discovery and design of therapeutic and diagnostic molecules. The crystal structure is useful to make a structural or computer model of the polypeptide, complex or its portion. (I) is also useful for determining crystal structure of a homolog of (P). A protein complex comprising (P) is useful for identifying modulators of the protein complex. Detecting the presence of (P) is useful for diagnosing a patient suffering from a disease or disorder of a pathogenic species. The diagnostic assays are useful for monitoring the effectiveness of an anti-pathogenic treatment in an individual suffering from a disease or disorder of such pathogen. (I) and the recombinant polypeptides are useful for inducing an immunological response in an individual and as an antigen for vaccination of a host to produce specific antibodies which protect against invasion of bacteria, for example by blocking adherence of bacteria to damaged tissue.

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Terms	Documents
L1 and crystal$8	8

Display Format: - Change Format

Previous Page Next Page

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=> file .nash
=> s pneumoniae and acyl carrier protein synthase and crystal?
L1             3 FILE MEDLINE
L2             5 FILE CAPLUS
L3             3 FILE SCISEARCH
L4             2 FILE LIFESCI
L5             2 FILE BIOSIS
L6             3 FILE EMBASE

TOTAL FOR ALL FILES
L7            18 PNEUMONIAE AND ACYL CARRIER PROTEIN SYNTHASE AND CRYSTAL?

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8             7 DUP REM L7 (11 DUPLICATES REMOVED)

=> d ibib abs 1-7

L8   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:         2003:261864  CAPLUS
DOCUMENT NUMBER:          138:282444
TITLE:                    Cloning, purification and characterization of
                          polypeptides from pathogenic bacteria involved in
                          membrane biosynthesis, and drug screening and drug
                          design applications
INVENTOR(S):              Edwards, Aled; Dharamsi, Akil; Vedadi, Masoud; Alam,
                          Muhammad Zahoor; Awrey, Donald; Beattie, Bryan;
                          Canadien, Veronica; Domagala, Megan; Houston, Simon;
                          Kanagarajah, Dhushy; Li, Qin; Mansoury, Kamran;
                          McDonald, Merry-Lynn; Necakov, Sasha; Ng, Ivy; Pinder,
                          Benjamin; Sheldrick, Bay; Vallee, Francois; Viola,
                          Cristina; Wrezel, Olga
PATENT ASSIGNEE(S):       Affinium Pharmaceuticals, Inc., Can.
SOURCE:                   PCT Int. Appl., 312 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.         KIND  DATE          APPLICATION NO.   DATE
     ---------------    ----  --------      ---------------   --------
     WO 2003027139       A2   20030403      WO 2002-CA1443    20020924
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD,
             RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
             NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2001-324449P  P  20010924
                                          US 2001-324504P  P  20010924
                                          US 2001-326269P  P  20011001
                                          US 2001-326887P  P  20011003
                                          US 2001-339560P  P  20011024
                                          US 2001-337471P  P  20011025
                                          US 2001-340000P  P  20011026
                                          US 2001-340002P  P  20011026
                                          US 2001-340027P  P  20011026
                                          US 2001-341767P  P  20011218
                                          US 2001-344307P  P  20011221
                                          US 2001-343946P  P  20011227
AB   The present invention relates to polypeptide targets for pathogenic
     bacteria.  A no. of antimicrobial target enzymes and proteins have been
     identified, expressed, and purified from Staphylococcus aureus,
     Helicobacter pylori, Streptococcus pneumoniae, and Pseudomonas
```

aeruginosa. Cloning, the nucleotide sequences and the encoded amino acid sequences of genes ftsZ, fabZ, acpS, murD, murC, fabH, tagD, obg, and fabG from S. aureus, H. pylori, S. **pneumoniae**, and P. aeruginosa are disclosed. The invention also provides biochem. and biophys. characteristics of those polypeptides. The polypeptides are characterized by using mass spectrometry, NMR, x-ray **crystallog.**, and bioinformatics anal. The polypeptides of the invention can be used for drug screening, drug design, in diagnostic assays and in pharmacol. applications.

L8 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:282044 CAPLUS
DOCUMENT NUMBER: 138:283319
TITLE: Purification, characterization and **crystal** structure of Streptococcus **pneumoniae** **acyl carrier protein** **synthase** for use in diagnostics, antibacterial drug design, and biosensors
INVENTOR(S): Chirgadze, Nicholas Yuri; Briggs, Stephen Lyle; Zhao, Genshi; McAllister, Kelly Ann
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 158 pp. CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003068802	A1	20030410	US 2001-897645	20010629

PRIORITY APPLN. INFO.: US 2000-215577P P 20000630

AB Provided are methods of purifying and **crystg.** Streptococcus **pneumoniae** **acyl carrier protein** **synthase** (AcpS) enzyme, **crystals** of AcpS, the use of such **crystals** to det. the three-dimensional structure of AcpS enzymes, and the three-dimensional structure of AcpS. The three-dimensional **crystal** structure of AcpS can be used in medical diagnostics to produce antibodies that permit detection of Streptococcus **pneumoniae** both in vitro and in vivo. The three-dimensional **crystal** structure of AcpS can also be used in pharmaceutical discovery and development to identify and design compds. that inhibit the biochem. activity of AcpS enzyme in bacteria. Inhibitory compds. identified in this way can be optimized by structure/activity studies to develop antibacterial pharmaceutical compds. useful for the prevention or treatment of bacterial infections.

L8 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003309674 MEDLINE
DOCUMENT NUMBER: 22721826 PubMed ID: 12837788
TITLE: The 1.3-Angstrom-resolution **crystal** structure of beta-ketoacyl-**acyl carrier** **protein synthase** II from Streptococcus **pneumoniae**.
AUTHOR: Price Allen C; Rock Charles O; White Stephen W
CORPORATE SOURCE: Department of Structural Biology, St. Jude Children's Research Hospital, Department of Molecular Sciences, University of Tennessee, Memphis, Tennessee 38105, USA.
CONTRACT NUMBER: CA21765 (NCI)
GM34496 (NIGMS)
SOURCE: JOURNAL OF BACTERIOLOGY, (2003 Jul) 185 (14) 4136-43. Journal code: 2985120R. ISSN: 0021-9193.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1OX0; PDB-1OXH
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030703
Last Updated on STN: 20030809
Entered Medline: 20030808

AB The beta-ketoacyl-**acyl carrier protein synthases** are members of the thiolase superfamily and are key regulators of bacterial fatty acid synthesis. As essential components of the bacterial lipid metabolic pathway, they are an attractive target for antibacterial drug discovery. We have determined the 1.3 A resolution **crystal** structure of the beta-ketoacyl-**acyl carrier protein synthase** II (FabF) from the pathogenic organism Streptococcus **pneumoniae**. The protein adopts a duplicated betaalphabetaalphabetaalphabetabeta fold, which is characteristic of the thiolase superfamily. The two-fold pseudosymmetry is broken by the presence of distinct insertions in the two halves of the protein. These insertions have evolved to bind the specific substrates of this particular member of the thiolase superfamily. Docking of the pantetheine moiety of the substrate identifies the loop regions involved in substrate binding and indicates roles for specific, conserved residues in the substrate binding tunnel. The active site triad of this superfamily is present in spFabF as His 303, His 337, and Cys 164. Near the active site is an ion pair, Glu 346 and Lys 332, that is conserved in the condensing enzymes but is unusual in our structure in being stabilized by an Mg(2+) ion which interacts with Glu 346. The active site histidines interact asymmetrically with Lys 332, whose positive charge is closer to His 303, and we propose a specific role for the lysine in polarizing the imidazole ring of this histidine. This asymmetry suggests that the two histidines have unequal roles in catalysis and provides new insights into the catalytic mechanisms of these enzymes.

L8 ANSWER 4 OF 7 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003051581 EMBASE
TITLE: Bacterial .beta.-ketoacyl-**acyl carrier protein synthases** as targets for antibacterial agents.
AUTHOR: Khandekar S.S.; Daines R.A.; Lonsdale J.T.
CORPORATE SOURCE: S.S. Khandekar, Department of Protein Biochemistry, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, United States. Sanjay_Khandekar-1@gsk.com
SOURCE: Current Protein and Peptide Science, (2003) 4/1 (21-29). Refs: 55
ISSN: 1389-2037 CODEN: CPPSCM
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB As a result of increasing drug resistance in pathogenic bacteria, there is a critical need for novel broad-spectrum antibacterial agents. As fatty acid synthesis (FAS) in bacteria is an essential process for cell survival, the enzymes involved in the FAS pathway have emerged as promising targets for antimicrobial agents. Several lines of evidence have indicated that bacterial condensing enzymes are central to the initiation and elongation steps in bacterial fatty acid synthesis and play a pivotal role in the regulation of the entire fatty acid synthesis pathway. .beta.-ketoacyl-acyl carrier protein (ACP) synthases (KAS) from various bacterial species have been cloned, expressed and purified in large quantities for detailed enzymological, structural and screening studies. Availability of purified KAS from a variety of bacteria, along with a combination of techniques, including combinatorial chemistry, high-throughput screening, and rational drug design based on **crystal** structures, will undoubtedly aid in the discovery and development of much needed potent and broad-spectrum antibacterial agents. In this review we summarize the biochemical, biophysical and inhibition properties of .beta.-ketoacyl-ACP synthases from a variety of bacterial species.

L8 ANSWER 5 OF 7 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2002739526 MEDLINE
DOCUMENT NUMBER: 22391025 PubMed ID: 12502353
TITLE: First X-ray cocrystal structure of a bacterial FabH condensing enzyme and a small molecule inhibitor achieved

using rational design and homology modeling.
AUTHOR: Daines Robert A; Pendrak Israil; Sham Kelvin; Van Aller Glenn S; Konstantinidis Alex K; Lonsdale John T; Janson Cheryl A; Qiu Xiayang; Brandt Martin; Khandekar Sanjay S; Silverman Carol; Head Martha S
CORPORATE SOURCE: Department of Medicinal Chemistry, GlaxoSmithKline, 1250 S. Collegeville Road, Collegeville, Pennsylvania 19426, USA.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2003 Jan 2) 46 (1) 5-8. Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1MZS
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021228
Last Updated on STN: 20030205
Entered Medline: 20030204

AB The first cocrystal structure of a bacterial FabH condensing enzyme and a small molecule inhibitor is reported. The inhibitor was obtained by rational modification of a high throughput screening lead with the aid of a S. **pneumoniae** FabH homology model. This homology model was used to design analogues that would have both high affinity for the enzyme and appropriate aqueous solubility to facilitate cocrystallization studies.

L8 ANSWER 6 OF 7 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2001:687481 SCISEARCH
THE GENUINE ARTICLE: 464XE
TITLE: Identification, substrate specificity, and inhibition of the Streptococcus **pneumoniae** beta-ketoacyl-**acyl carrier protein** **synthase** III (FabH)
AUTHOR: Khandekar S S (Reprint); Gentry D R; Van Aller G S; Warren P; Xiang H; Silverman C; Doyle M L; Chambers P A; Konstantinidis A K; Brandt M; Daines R A; Lonsdale J T
CORPORATE SOURCE: Glaxo SmithKline, Dept Prot Biochem, 709 Swedeland Rd, King Of Prussia, PA 19406 USA (Reprint); Glaxo SmithKline, Dept Prot Biochem, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Prot Biochem, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Biol Struct, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Bioinformat, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Mechanist Enzymol, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Med Chem, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Microbial Biochem, King Of Prussia, PA 19406 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (10 AUG 2001) Vol. 276, No. 32, pp. 30024-30030. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the bacterial type II fatty acid synthase system, beta -ketoacyl-acyl carrier protein (ACP) synthase IH (FabH) catalyzes the condensation of acetyl-CoA with malonyl-ACP. We have identified, expressed, and characterized the Streptococcus **pneumoniae** homologue of Escherichia coli FabH. S. **pneumoniae** FabH is similar to 41, 39, and 38% identical in amino acid sequence to Bacillus subtilis, E. coli and Hemophilus influenzae FabH, respectively. The His-Asn-Cys catalytic triad present in other FabH molecules is conserved in S. **pneumoniae** FabH. The apparent K-m values for acetyl-CoA and malonyl-ACP were determined to be 40.3 and 18.6 muM, respectively. Purified S. **pneumoniae** FabH preferentially utilized straight short-chain CoA primers. Similar to E. coli FabH, S. **pneumoniae** FabH was weakly inhibited by thiolactomycin. In contrast, inhibition of S. **pneumoniae** FabH by the newly developed compound SB418011 was very

potent, with an IC50 value of 0.016 muM. SB418011 also inhibited E. coli and H. influenzae FabH with IC50 values of 1.2 and. 0.59 muM, respectively. The availability of purified and characterized S. **pneumoniae** FabH will greatly aid in structural studies of this class of essential bacterial enzymes and. facilitate the identification of small molecule inhibitors of type II fatty acid synthase with the potential to be novel and potent antibacterial agents active against pathogenic bacteria.

L8 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001037762 MEDLINE
DOCUMENT NUMBER: 20490359 PubMed ID: 11032795
TITLE: **Crystal** structure of Streptococcus **pneumoniae acyl carrier protein synthase**: an essential enzyme in bacterial fatty acid biosynthesis.
AUTHOR: Chirgadze N Y; Briggs S L; McAllister K A; Fischl A S; Zhao G
CORPORATE SOURCE: Lilly Research Laboratories, Indianapolis, IN 46285, USA.. nyc@lilly.com
SOURCE: EMBO JOURNAL, (2000 Oct 16) 19 (20) 5281-7. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001128

AB **Acyl carrier protein synthase** (AcpS) catalyzes the formation of holo-ACP, which mediates the essential transfer of acyl fatty acid intermediates during the biosynthesis of fatty acids and lipids in the cell. Thus, AcpS plays an important role in bacterial fatty acid and lipid biosynthesis, making it an attractive target for therapeutic intervention. We have determined, for the first time, the **crystal** structure of the Streptococcus **pneumoniae** AcpS and AcpS complexed with 3'5'-ADP, a product of AcpS, at 2.0 and 1.9 A resolution, respectively. The **crystal** structure reveals an alpha/beta fold and shows that AcpS assembles as a tightly packed functional trimer, with a non-**crystallographic** pseudo-symmetric 3-fold axis, which contains three active sites at the interface between protomers. Only two active sites are occupied by the ligand molecules. Although there is virtually no sequence similarity between the S.**pneumoniae** AcpS and the Bacillus subtilis Sfp transferase, a striking structural similarity between both enzymes was observed. These data provide a starting point for structure-based drug design efforts towards the identification of AcpS inhibitors with potent antibacterial activity.

```
=> s pneumoniae and acyl carrier protein synthase and structure
L9            3 FILE MEDLINE
L10           4 FILE CAPLUS
L11           3 FILE SCISEARCH
L12           2 FILE LIFESCI
L13           2 FILE BIOSIS
L14           4 FILE EMBASE

TOTAL FOR ALL FILES
L15          18 PNEUMONIAE AND ACYL CARRIER PROTEIN SYNTHASE AND STRUCTURE

=> dup rem l15
PROCESSING COMPLETED FOR L15
L16           7 DUP REM L15 (11 DUPLICATES REMOVED)

=> d ibib abs 1-7

L16  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:         2003:282044  CAPLUS
DOCUMENT NUMBER:          138:283319
```

TITLE: Purification, characterization and crystal **structure** of Streptococcus **pneumoniae** **acyl carrier protein** **synthase** for use in diagnostics, antibacterial drug design, and biosensors
INVENTOR(S): Chirgadze, Nicholas Yuri; Briggs, Stephen Lyle; Zhao, Genshi; McAllister, Kelly Ann
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 158 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003068802	A1	20030410	US 2001-897645	20010629

PRIORITY APPLN. INFO.: US 2000-215577P P 20000630

AB Provided are methods of purifying and crystg. Streptococcus **pneumoniae acyl carrier protein** **synthase** (AcpS) enzyme, crystals of AcpS, the use of such crystals to det. the three-dimensional **structure** of AcpS enzymes, and the three-dimensional **structure** of AcpS. The three-dimensional crystal **structure** of AcpS can be used in medical diagnostics to produce antibodies that permit detection of Streptococcus **pneumoniae** both in vitro and in vivo. The three-dimensional crystal **structure** of AcpS can also be used in pharmaceutical discovery and development to identify and design compds. that inhibit the biochem. activity of AcpS enzyme in bacteria. Inhibitory compds. identified in this way can be optimized by **structure**/activity studies to develop antibacterial pharmaceutical compds. useful for the prevention or treatment of bacterial infections.

L16 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003309674 MEDLINE
DOCUMENT NUMBER: 22721826 PubMed ID: 12837788
TITLE: The 1.3-Angstrom-resolution crystal **structure** of beta-ketoacyl-**acyl carrier** **protein synthase** II from Streptococcus **pneumoniae.**
AUTHOR: Price Allen C; Rock Charles O; White Stephen W
CORPORATE SOURCE: Department of Structural Biology, St. Jude Children's Research Hospital, Department of Molecular Sciences, University of Tennessee, Memphis, Tennessee 38105, USA.
CONTRACT NUMBER: CA21765 (NCI)
GM34496 (NIGMS)
SOURCE: JOURNAL OF BACTERIOLOGY, (2003 Jul) 185 (14) 4136-43.
Journal code: 2985120R. ISSN: 0021-9193.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1OX0; PDB-1OXH
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030703
Last Updated on STN: 20030809
Entered Medline: 20030808

AB The beta-ketoacyl-**acyl carrier protein** **synthases** are members of the thiolase superfamily and are key regulators of bacterial fatty acid synthesis. As essential components of the bacterial lipid metabolic pathway, they are an attractive target for antibacterial drug discovery. We have determined the 1.3 A resolution crystal **structure** of the beta-ketoacyl-**acyl** **carrier protein synthase** II (FabF) from the pathogenic organism Streptococcus **pneumoniae**. The protein adopts a duplicated betaalphabetaalphabetaalphabetabeta fold, which is characteristic of the thiolase superfamily. The two-fold pseudosymmetry is broken by the presence of distinct insertions in the two halves of the protein. These insertions have evolved to bind the specific substrates of this particular member of the thiolase superfamily. Docking of the

pantetheine moiety of the substrate identifies the loop regions involved in substrate binding and indicates roles for specific, conserved residues in the substrate binding tunnel. The active site triad of this superfamily is present in spFabF as His 303, His 337, and Cys 164. Near the active site is an ion pair, Glu 346 and Lys 332, that is conserved in the condensing enzymes but is unusual in our **structure** in being stabilized by an Mg(2+) ion which interacts with Glu 346. The active site histidines interact asymmetrically with Lys 332, whose positive charge is closer to His 303, and we propose a specific role for the lysine in polarizing the imidazole ring of this histidine. This asymmetry suggests that the two histidines have unequal roles in catalysis and provides new insights into the catalytic mechanisms of these enzymes.

L16 ANSWER 3 OF 7 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003051581 EMBASE
TITLE: Bacterial .beta.-ketoacyl-**acyl carrier protein synthases** as targets for antibacterial agents.
AUTHOR: Khandekar S.S.; Daines R.A.; Lonsdale J.T.
CORPORATE SOURCE: S.S. Khandekar, Department of Protein Biochemistry, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, United States. Sanjay_Khandekar-1@gsk.com
SOURCE: Current Protein and Peptide Science, (2003) 4/1 (21-29). Refs: 55
ISSN: 1389-2037 CODEN: CPPSCM
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB As a result of increasing drug resistance in pathogenic bacteria, there is a critical need for novel broad-spectrum antibacterial agents. As fatty acid synthesis (FAS) in bacteria is an essential process for cell survival, the enzymes involved in the FAS pathway have emerged as promising targets for antimicrobial agents. Several lines of evidence have indicated that bacterial condensing enzymes are central to the initiation and elongation steps in bacterial fatty acid synthesis and play a pivotal role in the regulation of the entire fatty acid synthesis pathway. .beta.-ketoacyl-acyl carrier protein (ACP) synthases (KAS) from various bacterial species have been cloned, expressed and purified in large quantities for detailed enzymological, structural and screening studies. Availability of purified KAS from a variety of bacteria, along with a combination of techniques, including combinatorial chemistry, high-throughput screening, and rational drug design based on crystal **structures**, will undoubtedly aid in the discovery and development of much needed potent and broad-spectrum antibacterial agents. In this review we summarize the biochemical, biophysical and inhibition properties of .beta.-ketoacyl-ACP synthases from a variety of bacterial species.

L16 ANSWER 4 OF 7 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2002739526 MEDLINE
DOCUMENT NUMBER: 22391025 PubMed ID: 12502353
TITLE: First X-ray cocrystal **structure** of a bacterial FabH condensing enzyme and a small molecule inhibitor achieved using rational design and homology modeling.
AUTHOR: Daines Robert A; Pendrak Israil; Sham Kelvin; Van Aller Glenn S; Konstantinidis Alex K; Lonsdale John T; Janson Cheryl A; Qiu Xiayang; Brandt Martin; Khandekar Sanjay S; Silverman Carol; Head Martha S
CORPORATE SOURCE: Department of Medicinal Chemistry, GlaxoSmithKline, 1250 S. Collegeville Road, Collegeville, Pennsylvania 19426, USA.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2003 Jan 2) 46 (1) 5-8. Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1MZS

ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021228
Last Updated on STN: 20030205
Entered Medline: 20030204

AB The first cocrystal **structure** of a bacterial FabH condensing enzyme and a small molecule inhibitor is reported. The inhibitor was obtained by rational modification of a high throughput screening lead with the aid of a S. **pneumoniae** FabH homology model. This homology model was used to design analogues that would have both high affinity for the enzyme and appropriate aqueous solubility to facilitate cocrystallization studies.

L16 ANSWER 5 OF 7 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2001:687481 SCISEARCH
THE GENUINE ARTICLE: 464XE
TITLE: Identification, substrate specificity, and inhibition of the Streptococcus **pneumoniae** beta-ketoacyl-**acyl carrier protein** **synthase** III (FabH)
AUTHOR: Khandekar S S (Reprint); Gentry D R; Van Aller G S; Warren P; Xiang H; Silverman C; Doyle M L; Chambers P A; Konstantinidis A K; Brandt M; Daines R A; Lonsdale J T
CORPORATE SOURCE: Glaxo SmithKline, Dept Prot Biochem, 709 Swedeland Rd, King Of Prussia, PA 19406 USA (Reprint); Glaxo SmithKline, Dept Prot Biochem, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Prot Biochem, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Biol Struct, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Bioinformat, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Mechanist Enzymol, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Med Chem, King Of Prussia, PA 19406 USA; Glaxo SmithKline, Dept Microbial Biochem, King Of Prussia, PA 19406 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (10 AUG 2001) Vol. 276, No. 32, pp. 30024-30030.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the bacterial type II fatty acid synthase system, beta -ketoacyl-acyl carrier protein (ACP) synthase IH (FabH) catalyzes the condensation of acetyl-CoA with malonyl-ACP. We have identified, expressed, and characterized the Streptococcus **pneumoniae** homologue of Escherichia coli FabH. S. **pneumoniae** FabH is similar to 41, 39, and 38% identical in amino acid sequence to Bacillus subtilis, E. coli and Hemophilus influenzae FabH, respectively. The His-Asn-Cys catalytic triad present in other FabH molecules is conserved in S. **pneumoniae** FabH. The apparent K-m values for acetyl-CoA and malonyl-ACP were determined to be 40.3 and 18.6 muM, respectively. Purified S. **pneumoniae** FabH preferentially utilized straight short-chain CoA primers. Similar to E. coli FabH, S. **pneumoniae** FabH was weakly inhibited by thiolactomycin. In contrast, inhibition of S. **pneumoniae** FabH by the newly developed compound SB418011 was very potent, with an IC50 value of 0.016 muM. SB418011 also inhibited E. coli and H. influenzae FabH with IC50 values of 1.2 and. 0.59 muM, respectively. The availability of purified and characterized S. **pneumoniae** FabH will greatly aid in structural studies of this class of essential bacterial enzymes and. facilitate the identification of small molecule inhibitors of type II fatty acid synthase with the potential to be novel and potent antibacterial agents active against pathogenic bacteria.

L16 ANSWER 6 OF 7 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000357478 EMBASE
TITLE: Biochemical and molecular analyses of the Streptococcus **pneumoniae acyl carrier**

protein synthase, an enzyme essential for fatty acid biosynthesis.

AUTHOR: McAllister K.A.; Peery R.B.; Meier T.I.; Fischl A.S.; Zhao G.

CORPORATE SOURCE: G. Zhao, Lilly Research Laboratories, Infectious Diseases Research, Eli Lilly and Company, Indianapolis, IN 46285, United States

SOURCE: Journal of Biological Chemistry, (6 Oct 2000) 275/40 (30864-30872).
Refs: 47
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB **Acyl carrier protein synthase** (AcpS) is an essential enzyme in the biosynthesis of fatty acids in all bacteria. AcpS catalyzes the transfer of 4'-phosphopantetheine from coenzyme A (CoA) to apo-ACP, thus converting apo-ACP to holo-ACP that serves as an acyl carrier for the biosynthesis of fatty acids and lipids. To further understand the physiological role of AcpS, we identified, cloned, and expressed the acpS and acpP genes of Streptococcus **pneumoniae** and purified both products to homogeneity. Both acpS and acpP form operons with the genes whose functions are required for other cellular metabolism. The acpS gene complements an Escherichia coli mutant defective in the production of AcpS and appears to be essential for the growth of S. **pneumoniae**. Gel filtration and cross-linking analyses establish that purified AcpS exists as a homotrimer. AcpS activity was significantly stimulated by apo-ACP at concentrations over 10 .mu.M and slightly inhibited at concentrations of 5-10 .mu.M. Double reciprocal analysis of initial velocities of AcpS at various concentrations of CoA or apo-ACP indicated a random or compulsory ordered bi bi type of reaction mechanism. Further analysis of the inhibition kinetics of the product (3',5'-ADP) suggested that it is competitive with respect to CoA but mixed (competitive and noncompetitive) with respect to apo-ACP. Finally, apo-ACP bound tightly to AcpS in the absence of CoA, but CoA failed to do so in the absence of apo-ACP. Together, these results suggest that AcpS may be allosterically regulated by apo-ACP and probably proceeds by an ordered reaction mechanism with the first formation of the AcpS-apo-ACP complex and the subsequent transfer of 4'-phosphopantetheine to the apo-ACP of the complex.

L16 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2001037762 MEDLINE

DOCUMENT NUMBER: 20490359 PubMed ID: 11032795

TITLE: Crystal **structure** of Streptococcus **pneumoniae acyl carrier protein synthase**: an essential enzyme in bacterial fatty acid biosynthesis.

AUTHOR: Chirgadze N Y; Briggs S L; McAllister K A; Fischl A S; Zhao G

CORPORATE SOURCE: Lilly Research Laboratories, Indianapolis, IN 46285, USA.. nyc@lilly.com

SOURCE: EMBO JOURNAL, (2000 Oct 16) 19 (20) 5281-7.
Journal code: 8208664. ISSN: 0261-4189.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200011

ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001128

AB **Acyl carrier protein synthase** (AcpS) catalyzes the formation of holo-ACP, which mediates the essential transfer of acyl fatty acid intermediates during the biosynthesis of fatty acids and lipids in the cell. Thus, AcpS plays an important role in bacterial fatty acid and lipid biosynthesis, making it an attractive target for therapeutic intervention. We have determined, for the first

time, the crystal **structure** of the Streptococcus **pneumoniae** AcpS and AcpS complexed with 3'5'-ADP, a product of AcpS, at 2.0 and 1.9 A resolution, respectively. The crystal **structure** reveals an alpha/beta fold and shows that AcpS assembles as a tightly packed functional trimer, with a non-crystallographic pseudo-symmetric 3-fold axis, which contains three active sites at the interface between protomers. Only two active sites are occupied by the ligand molecules. Although there is virtually no sequence similarity between the S.**pneumoniae** AcpS and the Bacillus subtilis Sfp transferase, a striking structural similarity between both enzymes was observed. These data provide a starting point for **structure** -based drug design efforts towards the identification of AcpS inhibitors with potent antibacterial activity.

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